ACTA
STOMATOLOGICA
CROATICA
www.ascro.hr

Acta stomatol Croat. 2015;49(4):325-330.
DOI: 10.15644/asc49/4/8

PRETHODNO PRIOPĆENJE
PRELIMINARY COMMUNICATION

Mujgan Gungor Hatipoglu[1], Sermet Inal[2], Sahin Kabay[3], Muhammet Kasim Cayci[4], Ayşenur Deger[5], Halil Isa Kuru[6], Sayit Altikat[7], Gizem Akkas[8]

Utjecaj različitih nesteroidnih protuupalnih lijekova na alveolarnu kost štakora: eksperimentalno istraživanje

The Influence of Different Nonsteroidal Anti-Inflammatory Drugs on Alveolar Bone in Rats: An Experimental Study

[1] Zavod za dentalnu maksilofacijalnu radiologiju Stomatološkog fakulteta Sveučilišta Dumlupinar, Katahya, Turska
Department of Dentomaxillofacial Radiology, Faculty of Dentistry, Dumlupinar University, Kutahya, Turkey.
[2] Zavod za ortopediju i traumatologiju Medicinskog fakulteta Sveučilišta Dumlupinar, Kutahya, Turska
Department of Orthopaedic and Traumatology, Faculty of Medicine, Dumlupinar University, Kutahya. Turkey.
[3] Zavod za urologiju Medicinskog fakulteta Sveučilišta Dumlupinar, Kutahya, Turska
Department of Urology, Medical Faculty, Faculty of Medicine, Dumlupinar University, Kutahya, Turkey.
[4] Zavod za biologiju Fakulteta prirodnih znanosti Sveučilišta Dumlupinar Kutahya, Turska
Department of Biology, Faculty of Arts and Science, Dumlupinar University, Kutahya,Turkey..
[5] Zavod za patologiju Medicinskog fakulteta Sveučilišta Dumlupinar, Kutahya,Turska
Department of Pathology, Faculty of Medicine, Dumlupinar University, Kutahya,Turkey
[6] Zavod za medicinsku laboratorijsku tehnologiju Učilišta Simav Sveučilišta Dumlupinar, Kutahya, Turska
Department of Medical Laboratory Techniques, Simav Vocational High School, Dumlupinar University, Kutahya, Turkey
[7] Zavod za biokemiju Medicinskoga fakulteta Sveučilišta Dumlupinar, Kutahya, Turska
Department of Department of Biochemistry, Faculty of Medicine, Dumlupinar University, Kutahya, Turkey
[8] Zavod za patologiju Ministarstva zdravlja u sklopu Sveučilišta Dumlupinar i Kliničke bolnice u Kutahyi Turska
Department of Pathology, Ministry of Health, Dumlupinar University, Kutahya Evliya Celebi Education and Research Hospital, Kutahya, Turkey

Sažetak

Svrha ovog istraživanja bila je proučiti učinak deksketoprofen-trometamola, meloksikama i natrijeva diklofenaka na netretiranu alveolarnu kost kada se koriste lijekovi za neku drugu indikaciju. **Materijali i metode:** Dvadeset osam mužjaka štakora *Spraque-Dawley* randomizirano je u četiri grupe na sličan način: tretirani su deksketoprofen-trometamolom (grupa 1.), meloksikamom (grupa 2.) i natrijevim diklofenakom (grupa 3.), a u kontrolnoj grupi nije se primjenjivao nikakav lijek. Nesteroidne protuupalne lijekove (NSAID) dobivali su deset dana nakon frakture fibule. Netretiranoj alveolarnoj kosti histopatološki se procjenjivala gustoća spongiozne kosti te osteoklastična i osteoblastična gustoća. **Rezultati:** Gustoća spongiozne kosti bila je niža u eksperimentalnim grupama (grupe od 1 do 3) negoli u kontrolnoj ($p < 0,05$). Suprotno tome, u eksperimentalnim grupama uočeno je povećanje gustoće osteoklasta u odnosu prema kontrolnoj grupi ($p < 0,05$). Prema gustoći osteoblasta grupe 2 i 3 bile su niže od kontrolne ($p < 0,05$), ali je u grupi 1 gustoća bila ista kao i u kontrolnoj. **Zaključak:** Ovo istraživanje pokazalo je da sustavno korištenje NSAID-a može utjecati na netretiranu alveolarnu kost. To se treba uzeti u obzir u slučaju produljenog korištenja tih lijekova.

Zaprimljen: 7. kolovoza 2015.
Prihvaćen: 23. listopada 2015.

Adresa za dopisivanje
Mujgan Gungor Hatipoglu
Dumlupinar University
Faculty of Dentistry
Department of Dentomaxillofacial Radiology
Kutahya, Turkey
mujgan121@yahoo.com

Ključne riječi
nesteroidni protuupalni lijekovi; pregradnja kosti; osteoblasti; osteoklasti; maksilarna kost

Uvod

Koštana pregradnja cjeloživotni je proces. Pritom osteoblasti i osteoklasti sudjeluju u stvaranju i razgradnji kosti. Njihov broj i aktivnost određuju mnogobrojni čimbenici, poput hormona i citokina te lokalno izlučene signalne molekule pod utjecajem mehaničkih stimulansa (1 – 3). Sistemski i nesistemski čimbenici koji utječu na koštano remodeliranje objašnjeni su u literaturi (4). U ove procese uključeni su različiti čimbenici te lokalni endokrini i parakrini faktori. Istaknimo da je korištenje nekoliko farmakoloških agenata najvažnije za zacjeljivanje kosti (5). Steroidi, kemoterapijski

Introduction

"Bone remodeling" is a dynamic process and continues throughout life. Osteoblasts and osteoclasts take part in bone formation and the destruction of the bone in this process. The number and activity of osteoclasts and osteoblasts are scheduled by a multitude of factors, such as hormones, cytokines and locally produced signaling molecules under the influence of mechanical stimuli (1-3). Systemic and non-systemic factors that affect bone remodeling are explained in the literature (4). Various systemic and local endocrine and paracrine factors are involved in these processes. One of the most im-

lijekovi i neke vrste antibiotika negativno utječu na cijeljenje kosti (5). Nesteroidni protuupalni lijekovi (NSAID) uobičajeni su medikamenti za uklanjanje bolova i upala, ali otkriveno je da mogu odgoditi i spriječiti zacjeljivanje koštanih lomova (5). Svrha ovog istraživanja bila je istražiti učinak deksketoprofen-trometamola (DEXT), meloksikama (MEL) i natrijeva diklofenaka (DIC) na alveolarnu kost kada se koriste u različite svrhe, kao što je prevencija boli bilo gdje u tijelu.

Materijali i metode

Eksperimentalne protokole odobrilo je Etičko povjerenstvo naše ustanove. Potrebne životinje kupljene su u Centru za medicinsko i kirurško istraživanje, a držane su u polikarbonatnim kavezima u prostoriji s kontroliranom temperaturom (22 ± 2°C) i potrebnom vlažnošću (50 ± 5%). Tijekom 12-satnih ciklusa noći i dana, hranjene su laboratorijskom hranom u peletima, a pile su vodu kada su bile žedne. Eksperiment je proveden nakon 15-dnevnog stabilizacijskog razdoblja u laboratoriju. Svi štakori korišteni u pokusima bili su tretirani prema smjernicama za brigu i korištenje laboratorijskih životinja te u skladu s preporukama Helsinške deklaracije.

Za procjenu netretiranih uzoraka maksile uzeti su štakori iz prije provedenog istraživanja (6). Za potrebe ovog istraživanja randomizirano je 28 mužjaka štakora *Spraque-Dawley* (250 – 300 g) u četiri grupe – po sedam u svakoj. Na svima je obavljen standardizirani zatvoreni frakturni model na fibulama. Jedan dan nakon stvorene frakture po grupama su dobivali NSAID-e: deksketoprofen-trometamol dobivali su oni u grupi 1 – 0,98 mg/kg 2 puta na dan; meloksikamom tretirane su životinje u grupi 2 – 0,2 mg/kg na dan, a natrijev diklofenak davao se grupi 3 – 1mg/kg na dan. Kontrolna grupa nije dobila ni jedan farmakološki spoj nakon frakture fibule učinjene prema istom protokolu. Kod svih eksperimentalnih grupa NSAID-i su primjenjivani u kliničkim dozama parenteralno deset dana nakon frakture. Nije bila primijenjena nikakva terapija ni zahvat na alveolarnoj kosti štakora. Uzeti su uzorci maksilarne alveolarne kosti te su fiksirani u 10-postotnoj otopini formalina, a meko tkivo sljedeći je dan uklonjeno. Nakon toga bili su dva dana uronjeni u 10-postotnu nitritnu kiselinu. Dekalcificirani uzorci ispirali su se dva sata u tekućoj vodi kako bi se uklonili ostatci kiseline. Svaki uzorak bio je podijeljen tako da se otkrije spoj, a primijenjen je rutinski postupak uklapanja. Na kraju su uzorci uklopljeni u parafin izrezani na 4 µm, prerezi su obojeni hematoksilin-eozinom te promatrani pod svjetlosnim mikroskopom (Olympus CX 41). Alveolarnim kostima procijenjena je gustoća spongiozne kosti te osteoklastična i osteoblastična gustoća, a zatim su uspoređivane među grupama. Svaka značajka posebno je klasificirana. Omjer gustoće spongiozne kosti i ukupne trabekularne kosti procjenjivao se na poprečnom presjeku (1: manje od 10 %; 2: između 10 % i 20 %; 3: više od 20 %). Gustoća osteoblasta određena je brojenjem oko koštanih

portant factors in bone healing is the use of several pharmacological agents (5). Steroids, chemotherapy drugs, and some classes of antibiotics have been reported to have negative effects on bone healing (5). Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed drugs for pain relief and inflammation but have also been found to have a potential to delay and to inhibit fracture healing (5).

The aim of this study was to investigate the indirect effects of dexketoprofen trometamol (DEXT), meloxicam (MEL) and diclofenac sodium (DIC) on alveolar bone when they are used for miscellaneous purposes such as prevention of pain anywhere in the body.

Materials and methods

The experimental protocols were approved by the institutional animal ethics committee. Animals were obtained from the medical and surgical experimental research center of the institute. All rats were housed in polycarbonate cages in a room with controlled temperature (22 ± 2°C), humidity (50 ± 5%), and a 12 hour cycle of light and dark and were fed laboratory pellet chows and water was given ad libitum. The experiment was performed after a stabilization period in the laboratory for fifteen days. All the rats used in the following experiments were subject to the Guiding Principles for the Care and Use of Laboratory Animals and the Recommendations of the Declaration of Helsinki.

The evaluated untreated specimens from rat maxillas were obtained from a previously performed study (6). In this study, 28 male Spraque-Dawley rats (250-300 g) were randomized into four groups of seven each. Unilateral standardized closed fracture model was performed in fibulas of all rats. The NSAIDs: dexketoprofen trometamol; administered to group I, 0.98 mg/kg per half a day, meloxicam; administered to Group II, 0.2 mg/kg per day and diclofenac sodium; administered to Group III, 1mg/kg per day after performing the fibular fractures. No pharmacological agent was administered to the control group after performing the fibular fractures. The NSAIDs were applied to all groups for the first 10 days parenterally after the occurrence of the fractures in clinical dosages. Any procedure or treatment was not performed in rat alveolar bones. Maxillary alveolar bone was removed from the rats. The bone specimens were first immersed in a 10 % formalin solution and the soft tissues separated from the bone the following day. Afterwards they were put into a 10% nitric acid solution for 2 days. The samples which decalcified were washed under the flowing water for 2 hours to remove acid residue. Each sample was divided to expose the union and routine tissue follow-up procedures were carried out. At the end; the paraffin embedded tissues were cut into slices 4 µm thick, stained with hematoxylin eosin and were observed under the light microscopy (Olympus CX41). The alveolar bones were evaluated for their spongious bone density, and the osteoclastic and osteoblastic densities were compared between the different experimental groups. Each parameter was classified separately. The ratio of spongious bone density to a total trabecular bone observed in cross section was evaluated (1, less than 10%; 2, between 10%

lamela u područjima aktivno-intenzivne proliferacije (povećanje 3 x) (1: 24 ili manje osteoblasta; 2: 25 do 34 osteoblasta; 3: 35 ili više osteoblasta). Gustoća osteoklasta određena je brojenjem oko koštanih lamela: (1: prosjek od f 3 ili manje osteoklasta; 2: prosjek od 4 do 6 osteoklasta; 3: prosjek od 7 ili više osteoklasta) (7).

Statistička analiza

Za statističku analizu korišten je kompjutorski program SPSS, Windows, 11.5 (Chicago, IL, SAD.). Izračunate su srednje vrijednosti i standardna devijacija. Za analizu homogenosti varijance korišten je Levenov test. Ako varijance nisu bile homogene, razlika je raščlanjena Kruskal-Wallisovom analizom varijance, a bilateralna usporedba rađena je Mann-Whitneyjevim U-testom. Kada su varijance bile distribuirane normalno, korišten je t-test za uparene uzorke. Razlike su se smatrale statistički značajnima pri $p < 0,05$.

Rezultati

Pronađene su statističke razlike (tablica 1.). Ustanovili smo da je gustoća spongiozne kosti bila statistički značajno niža u grupama DEXT, MEL i DIC u usporedbi s kontrol-

and 20%; 3, more than 20%). Osteoblast density was determined through counting of the osteoblasts around the bone lamellae in the active-intense proliferation area (3× magnification) (1, 24 or fewer osteoblasts; 2, 25-34 osteoblasts; 3, 35 or more osteoblasts). Osteoclast activity was determined through counting of the osteoclasts around the bone trabeculae (1, average of 3 or fewer osteoclasts; 2, average of 4-6 osteoclasts; 3, average of 7 or more osteoclasts) (7).

Statistical Analysis

A computer program was used for the statistical analysis (SPSS, Windows, 11.5, Chicago, IL, USA.). Mean and standard deviation were calculated. The Levene's test was used to analyze the homogeneity of the variances. If variances were not homogenous, the differences were analyzed using the Kruskal-Wallis variance analysis, bilateral comparisons were made by Mann- Whitney U test. The *t* test for paired samples was used when the variances distributed normally. Differences were considered statistically significant at $p<0.05$.

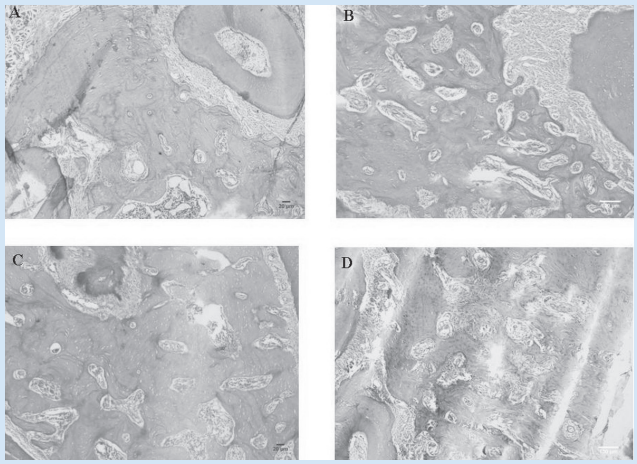
Results

Statistical differences were observed (Table 1). We found that spongious bone densities were statistically significantly decreased in groups DEXT, MEL, and DIC compared to the

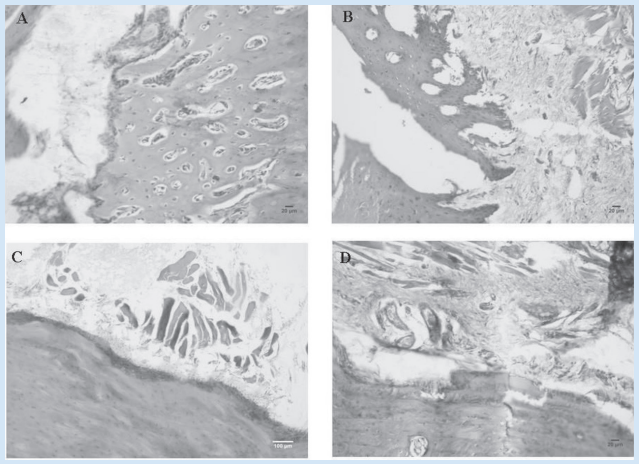
Tablica 1 Opisni podatci aritmetičkih sredina, standardne devijacije i p-vrijednosti o gustoći spongiozne kosti te gustoći osteoklasta i osteoblasta
Table 1 He descriptive data of the mean values, standard deviations and p-values related to spongious bone density, osteoclast and osteoblast densities.

Mjereni parametar • Parameter	Grupa • Groups	Aritmetička sredina ± S.D • Mean ± S.D	Usporedba • Comparison	
	GRUPA 1 • GROUP I	2.00 ± 0.81	Grupe • Groups	p
			GRUPA 1 – GRUPA 2 • GROUP I-GROUP II	0.164
	GRUPA 2 • GROUP II	1.42 ± 0.53	GRUPA1 — GRUPA 3 • GROUP I-GROUP III	0.293
Gustoća spongiozne kosti • Spongious Bone Density			GRUPA 1 – KONTROLA • GROUP I-CONTROL	0.009*
	GRUPA 3 • GROUP III	1.57 ± 0.53	GRUPA 2 – GRUPA 3 • GROUP II-GROUP III	0.606
			GRUPA 2 –- KONTROLA • GROUP II-CONTROL	0.001*
	KONTROLA • CONTROL	3.00 ± 0.00	GRUPA 3 – KONTROLA • GROUP III-CONTROL	0.001*
	GRUPA 1 • GROUP I	1.57 ± 0.53	Grupe • Groups	p
			GRUPA 1 – GRUPA 2 • GROUP I-GROUP II	0.293
	GRUPA 2 • GROUP II	2.00 ± 0.81	GRUPA1 — GRUPA 3 • GROUP I-GROUP III	0.424
Gustoća osteoklasta • Osteoclast Density			GRUPA 1 – KONTROLA • GROUP I-CONTROL	0.023*
	GRUPA 3 • GROUP III	1.85 ± 0.69	GRUPA 2 – GRUPA 3 • GROUP II-GROUP III	0.728
			GRUPA 2 –- KONTROLA • GROUP II-CONTROL	0.009*
	KONTROLA • CONTROL	1.00 ± 0.00	GRUPA 3 – KONTROLA • GROUP III-CONTROL	0.008*
	GRUPA 1 • GROUP I	2.28 ± 0.75	Grupe • Groups	p
			GRUPA 1 – GRUPA 2 • GROUP I-GROUP II	0.031*
	GRUPA 2 • GROUP II	1.42 ± 0.53	GRUPA1 — GRUPA 3 • GROUP I-GROUP III	0.012*
Gustoća osteoblasta • Osteoblast Density			GRUPA 1 – KONTROLA • GROUP I-CONTROL	1.00**
	GRUPA 3 • GROUP III	1.28 ± 0.48	GRUPA 2 – GRUPA 3 • GROUP II-GROUP III	0.611
			GRUPA 2 –- KONTROLA • GROUP II-CONTROL	0.009*
	KONTROLA • CONTROL	2.28 ± 0.48	GRUPA 3 – KONTROLA • GROUP III-CONTROL	0.002*

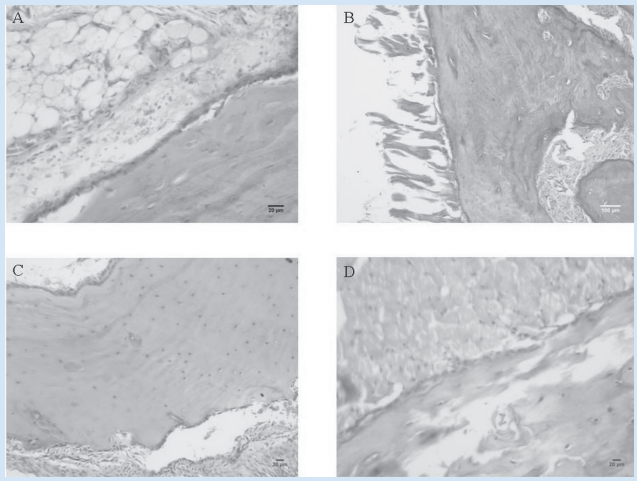
Levenov test korišten je za analizu homogenosti varijance. Ako varijance nisu bile homogene, razlike su analizirane Kruskal-Wallisovom analizom varijance, bilateralna usporedba obavljena je Mann-Whitneyjevim U-testom. *t* test za uparene uzorke korišten je kada su varijance raspoređene normalno. S.D.: standardna devijacija, * $p < 0,05$ značajno, ** $p = 1,00$ jednako, GRUPA 1: DEXT; GRUPA 2: MEL; GRUPA 3: DIC
The Levene test was used to analyze the homogeneity of the variances. If variances were not homogenous, the differences were analyzed using the Kruskal-Wallis variance analysis, bilateral comparisons were made by Mann- Whitney U test. The *t* test for paired samples was used when the variances distributed normally. S.D.: Standard Deviation, * $p<0.05$ significant, ** $p=1.00$ equal, GROUP I: DEXT; GROUP II: MEL; GROUP III: DIC



Slika 1. Histološki uzorci spongiozne kosti
A: grupa 1 (povećanje 200 x), B: grupa 2 (povećanje 100 x), C: grupa 3 (povećanje 200 x), D: kontrola grupa (povećanje 100 x)
Figure 1 Histological specimen of spongious bone
A: Group I (200x magnification), B: Group II (100x magnification), C: Group III (200x magnification), D: Control (100x magnification)



Slika 2. Histološki uzorci spongiozne kosti za gustoću osteoklasta
A: grupa 1 (povećanje 200 x), B: grupa 2 (povećanje 200 x), C: grupa 3 (povećanje 100 x), D: kontrola (povećanje 200 x)
Figure 2 Histological specimen of spongious bone osteoclast density
A: Group I (200x magnification), B: Group II (200x magnification), C: Group III (100x magnification), D: Control (200x magnification)



Slika 3. Histološki uzorci spongiozne kosti za gustoću osteoblasta
A: grupa 1 (povećanje 400 x), B: grupa 2 (povećanje 100 x), C: grupa 3 (povećanje 200 x), D: kontrola (povećanje 200 x)
Figure 3 Histological specimen of spongious bone osteoblast density
A: Group I (400x magnification), B: Group II (100x magnification), C: Group III (200x magnification), D: Control (200x magnification)

nom grupom ($p < 0,05$). (Slika 1). Suprotno tome, gustoća osteoklasta bila je statistički značajno viša u grupama DEXT, MEL, i DIC u odnosu prema kontrolnoj grupi ($p < 0,05$) (slika 2.). Gustoća osteoblasta pokazivala je statistički značajno manju vrijednost u grupama MEL i DIC u odnosu prema kontrolnoj grupi ($p < 0,05$) (slika 3.), a grupa DEXT bila je ista kao i kontrolna ($p = 1,00$) (tablica 1.). Grupa DEXT je u usporedbi s grupama MEL i DIC bila konzistentnija.

Rasprava

U ovom istraživanju pokazano je da sustavno davanje NSAID-a u druge svrhe može utjecati na strukturu alveolarne kosti indirektno na staničnoj razini. Nema istraživanja o posrednom utjecaju nesteroidnih protuupalnih lijekova na strukturu alveolarne kosti (osteoblastična/osteoklastična gustoća) tijekom korištenja lijekova u slučaju neke druge bolesti. U ovom istraživanju, za razliku od drugih, nije bilo nikakvog procesa ili stimulansa na alveolarnoj kosti, ali čini se da

control group ($p < 0.05$) (Figure 1). In contrast, osteoclastic densities were found to be statistically significantly higher in groups DEXT, MEL, and DIC than in the control group ($p < 0.05$) (Figure 2). The osteoblastic densities showed that there was a statistically significant decrease in groups MEL and DIC compared to the control group ($p < 0.05$) (Figure 3). Osteoblastic density in group DEXT was equal to the control group ($p = 1.00$) (Table 1). The DEXT group, compared to the MEL and DIC groups, seemed more consistent.

Discussion

This study showed that systemically administrated NSAIDs for other purposes have the potential to affect the alveolar bone structure indirectly at the cellular level.

There are no studies about the indirect effects of NSAIDs on alveolar bone structure (osteoblastic/osteoclastic densities) during the use of drugs for any other purposes. In this study, as opposed to other studies, there has not been any process or stimulus performed to the alveolar bone. Never-

nesteroidni protuupalni lijekovi utječu na alveolarnu kost. U literaturi, koja se obično dopunjuje istraživanjima u ortopediji, opsuju se neka istraživanja na životinjama o učinku ketoprofena, indometacina, ibuprofena, MEL-a, kelekoksiba, rofekoksiba i diklofenaka na cijeljenje kosti. U nekima od njih ističe se da ti lijekovi sprječavaju cijeljenje kosti, ali u dugima se kaže da to nije točno (8 – 17). Dodatno je pokazano da NSAID (niska doza diklofenaka) kod štakora sprječava heterotopičnu osifikaciju (18).

Trenutačno je u tijeku nekoliko istraživanja u području dentalne medicine, a usmjerena su na ovaj cilj. U nekim eksperimentalnim studijama autori su izvijestili o učinku konvencionalnih NSAID-a na cijeljenje alveolarne kosti (19 – 23). U histološkom istraživanju na ekstrakcijskim ranama pasa, uočeno je da korištenje aspirina uzrokuje kašnjenje u formiranju alveolarne kosti u uzorcima prva dva tjedna. Dugoročni učinak nije zapažen (4 – 8 tjedana) (20). Yugoshi i suradnici (21) izvijestili su da terapija diklofenakom uzrokuje znatno kašnjenje u neoformaciji kosti u procesu alveolarnog popravka. Silva i njegovi kolege (22) pokazali su da DIC i MEL uzrokuju kašnjenje u zacjeljivanja koštanoga presatka, a deksametazon nije imao učinka. Ketorolak i etorikoksib nisu utjecali na cijeljenje alveolarne kosti štakora dva tjedna nakon vađenja zuba (23). Teofilo i suradnici. (19) sugeriraju da kratkoročna terapija nimesulidom ne sprječava cijeljenje alveolarne kosti štakora. Knop i kolege (24) istaknuli su da diklofenak i deksametazon zaustavljaju koštanu resorpciju tijekom inicijalne faze ortodontskog pomicanja zuba.

Kakao je već istaknuto, u ovom istraživanju nije bilo nikakvog procesa.

NSAID-i utječu na životni ciklus osteoblastnih stanica i staničnu smrt. Neka istraživanja pokazala su da u terapijskim dozama djeluju na osteoblaste (25 – 27).

Ovo istraživanje pokazalo je da je gustoća osteoblasta bila značajno niža u grupama MEL i DIC u usporedbi s kontrolnom grupom. Najvažniji dio našeg rada, u odnosu prema drugim istraživanjima na alveolarnom nastavku, jest da nije bilo nikakvih procesa ni stimulansa tijekom korištenja nesteroidnih protuupalnih lijekova. Ovo bi se trebalo uzeti u razmatranje pri dugoročnom korištenju NSAID-a, primjerice kod pacijenata s ankiloznim spondilitisom (reumatska bolest). Smatramo da procjena posrednog učinka dugoročnog korištenja NSAID-a na druge tkivne strukture treba potaknuti daljnja istraživanja.

Sukob interesa

Nije bilo sukoba interesa.

theless, NSAID use appears to affect the alveolar bone.

In the literature, which has generally benefited from studies in orthopedics, there are some animal studies about the effects of ketoprofen, indomethacin, ibuprofen, MEL, celecoxib, rofecoxib, and diclofenac on bone healing. Some of these studies showed that these drugs impaired bone healing, but other studies showed that they did not affect the healing processes (8-17). In addition, NSAIDs (a low dose of diclofenac) have been shown to prevent heterotopic ossification in rats (18).

Presently, there are a few studies devoted to this subject in dentistry. A small number of experimental studies have reported the effect of conventional NSAIDs on alveolar bone healing (19-23). In a histological study performed on the extraction sockets of dogs, it was reported that using aspirin cones presented a delay in alveolar bone formation in the first 2 weeks' samples. But no effects were reported in the long term (4-8 weeks) (20). Yugoshi et al. (21) reported that treatment with diclofenac caused significant delay of bone neoformation in the alveolar repair process. Silva et al. (22) showed that DIC and MEL delayed bone graft repair and dexamethasone had no influence. Ketorolac and etoricoxib did not interfere with rat alveolar bone repair 2 weeks after tooth extraction (23). Teofilo et al. (19) suggested that a short-term treatment with nimesulide did not hinder alveolar bone healing in rats. Knop et al. (24) reported that diclofenac and dexamethasone halted bone resorption during the initial phase of orthodontic movement. As emphasized earlier in this study, there have not been any processes.

NSAIDs have an effect on the osteoblastic cell cycle and cell death. Some studies have shown that NSAIDs influence osteoblasts at therapeutic doses (25-27).

This study shows that osteoblastic density was significantly decreased in groups MEL and DIC compared to the control group. The most distinctive feature of our work in relation to other studies into the alveolar bone was that no process or stimulus was applied during the use of NSAIDs. This should be considered in the long-term use of NSAIDs, such as in ankylosing spondylitis patients (rheumatic diseases). We believe that the evaluation of indirect effects of the long-term use of NSAIDs on other tissue structures has potential for further scientific research.

Conflict of interest

None declared

Abstract

The aim: The aim of this study was to investigate the effect of dexketoprofen trometamol, meloxicam, diclofenac sodium on any untreated alveolar bone when they are used as drugs for another indication. **Materials and Methods:** Twenty eight male Spraque-Dawley rats were randomized into four groups as dexketoprofen trometamol (Group I), meloxicam (Group II), diclofenac sodium (Group III) and control group. Nonsteroidal anti-inflammatory drugs (NSAID) were administered after a fibula fracture for 10 days. Untreated alveolar bone was histopathologically examined for spongious bone density, osteoclastic density and osteoblastic density. **Results:** Spongious bone density was lower in study groups (Group I, group II and group III) than the control group ($p<0.05$). In contrast, the increase in osteoclastic density was observed in other groups apart from the control group ($p<0.05$). Osteoblastic density was evaluated and it was determined that group II and group III had lower results than the control group ($p<0.05$) but group I was equal to the control group. **Conclusion:** This study showed that systemically administrated NSAIDs have the potential to affect untreated alveolar bone. This should also be considered in long term use of NSAIDs.

Received: August 7, 2015
Accepted: October 23, 2015

Address for correspondence
Mujgan Gungor Hatipoglu
Dumlupinar University
Faculty of Dentistry
Department of Dentomaxillofacial Radiology
Kutahya, Turkey
mujgan121@yahoo.com

Key words
Non-Steroidal Anti-Inflammatory Agents; Bone Remodeling; Osteoblasts; Osteoclasts; maxilla

References

1. Vezeridis PS, Semeins CM, Chen Q, Klein-Nulend J. Osteocytes subjected to pulsating fluid flow regulate osteoblast proliferation and differentiation. Biochem Biophys Res Commun. 2006 Sep 29;348(3):1082-8.
2. You L, Temiyasathit S, Lee P, Kim CH, Tummala P, Yao W et al. Osteocytes as mechanosensors in the inhibition of bone resorption due to mechanical loading. Bone. 2008 Jan;42(1):172-9.
3. Onal M, Xiong J, Chen X, Thostenson JD, Almeida M, Manolagas SC et al. Receptor activator of nuclear factor κB ligand (RANKL) protein expression by B lymphocytes contributes to ovariectomy-induced bone loss. J Biol Chem. 2012 Aug 24;287(35):29851-60.
4. Painter SE, Kleerekoper M, Camacho PM. Secondary osteoporosis: a review of the recent evidence. Endocr Pract. 2006 Jul-Aug;12(4):436-45.
5. Pountos I, Georgouli T, Blokhuis TJ, Pape HC, Giannoudis PV. Pharmacological agents and impairment of fracture healing: what is the evidence? Injury. 2008 Apr;39(4):384-94.
6. Inal S, Kabay S, Cayci MK, Kuru HI, Altikat S, Akkas G, Deger A. Comparison of the effects of dexketoprofen trometamol, meloxicam and diclofenac sodium on fibular fracture healing, kidney and liver: An experimental rat model. Injury. 2014 Mar;45(3):494-500.
7. Alikaya C. Histopathological assessment of local application of alendronate combined with ABM/P-15 in bony defects [dissertation]. Ankara: Baskent University, Institute of Health Science; 2006.
8. Beck A, Krischak G, Sorg T, Augat P, Farker K, Merkel U et al. Influence of diclofenac (group of nonsteroidal anti-inflammatory drugs) on fracture healing. Arch Orthop Trauma Surg. 2003 Sep;123(7):327-32.
9. Sen C, Erdem M, Gunes T, Koseoglu D, Filiz NO. Effects of diclofenac and tenoxicam on distraction osteogenesis. Arch Orthop Trauma Surg. 2007 Apr;127(3):153-9.
10. Martins MV, da Silva MA, Medici Filho E, de Moraes LC, Castilho JC, da Rocha RF. Evaluation of digital optical density of bone repair in rats medicated with ketoprofen. Braz Dent J. 2005;16(3):207-12.
11. Urrutia J, Mardones R, Quezada F. The effect of ketoprophen on lumbar spinal fusion healing in a rabbit model. Laboratory investigation. J Neurosurg Spine. 2007 Dec;7(6):631-6.
12. van der Heide HJ, Hannink G, Buma P, Schreurs BW. No effect of ketoprofen and meloxicam on bone graft ingrowth: a bone chamber study in goats. Acta Orthop. 2008 Aug;79(4):548-54.
13. Sato S, Kim T, Arai T, Maruyama S, Tajima M, Utsumi N. Comparison between the effects of dexamethasone and indomethacin on bone wound healing. Jpn J Pharmacol. 1986 Sep;42(1):71-8.
14. Altman RD, Latta LL, Keer R, Renfree K, Hornicek FJ, Banovac K. Effect of nonsteroidal antiinflammatory drugs on fracture healing: a laboratory study in rats. J Orthop Trauma. 1995;9(5):392-400.
15. O'Connor JP, Capo JT, Tan V, Cottrell JA, Manigrasso MB, Bontempo N et al. A comparison of the effects of ibuprofen and rofecoxib on rabbit fibula osteotomy healing. Acta Orthop. 2009 Oct;80(5):597-605.
16. Herbenick MA, Sprott D, Stills H, Lawless M. Effects of a cyclooxygenase 2 inhibitor on fracture healing in a rat model. Am J Orthop (Belle Mead NJ). 2008 Jul;37(7):E133-7.
17. Adolphson P, Abbaszadegan H, Jonsson U, Dalén N, Sjöberg HE, Kalén S. No effects of piroxicam on osteopenia and recovery after Colles' fracture. A randomized, double-blind, placebo-controlled, prospective trial. Arch Orthop Trauma Surg. 1993;112(3):127-30.
18. Risto O, Wahlström O, Abdiu A. The effect of low dose diclofenac sodium administered locally on heterotopic bone formation in rats. Int Orthop. 1995;19(6):392-5.
19. Teófilo JM, Giovanini GS, Fracon RN, Lamano T. Histometric study of alveolar bone healing in rats treated with the nonsteroidal anti-inflammatory drug nimesulide. Implant Dent. 2011 Apr;20(2):e7-13.
20. Baratieri A, Deli R. The effect on bone repair of aspirin cones placed in extraction sockets in dogs: a histopathologic study. J Oral Pathol. 1979 Aug;8(4):198-206.
21. Yugoshi LI, Sala MA, Brentegani LG, Lamano Carvalho TL. Histometric study of socket healing after tooth extraction in rats treated with diclofenac. Braz Dent J. 2002;13(2):92-6.
22. Silva RA, Fagundes DJ, Antoniolli Silva AC, Sisti KE, Brochado de Carvalho TM, Silva DN. Effect of anti-inflammatory agents on the integration of autogenous bone graft and bovine bone devitalized matrix in rats. Acta Cir Bras. 2008 Mar-Apr;23(2):140-8.
23. Fracon RN, Teófilo JM, Moris IC, Lamano T. Treatment with paracetamol, ketorolac or etoricoxib did not hinder alveolar bone healing: a histometric study in rats. J Appl Oral Sci. 2010 Dec;18(6):630-4
24. Knop LA, Shintcovsk RL, Retamoso LB, Ribeiro JS, Tanaka OM. Non-steroidal and steroidal anti-inflammatory use in the context of orthodontic movement. Eur J Orthod. 2012 Oct;34(5):531-5.
25. García-Martínez O, Díaz-Rodríguez L, Rodríguez-Pérez L, De Luna-Bertos E, Reyes Botella C, Ruiz CC. Effect of acetaminophen, ibuprofen and methylprednisolone on different parameters of human osteoblast-like cells. Arch Oral Biol. 2011 Apr;56(4):317-23.
26. Krischak GD, Augat P, Blakytny R, Claes L, Kinzl L, Beck A. The non-steroidal anti-inflammatory drug diclofenac reduces appearance of osteoblasts in bone defect healing in rats. Arch Orthop Trauma Surg. 2007 Aug;127(6):453-8.
27. Etcheverry, SB, Barrio DA, Cortizo AM, Williams PAM. Three new vanadyl (IV) complexes with non-steroidal anti-inflammatory drugs (Ibuprofen, Naproxen and Tolmetin). Bioactivity on osteoblast-like cells in culture. J Inorg Biochem. 2002 Jan 1;88(1):94-100.